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Paschalides et al.

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(54) **CRYSTALLINE FORMS OF MORPHINE SULFATE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

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Related U.S. Application Data

(63) Continuation of application No. 14/670,493, filed on Mar. 27, 2015, now Pat. No. 9,145,420.

(51) **Int. Cl.**
C07D 489/04 (2006.01)

(52) **U.S. Cl.**
CPC **C07D 489/04** (2013.01); **C07B 2200/13** (2013.01)

(58) **Field of Classification Search**
USPC 546/44
See application file for complete search history.

(56) **References Cited**

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Primary Examiner — Charanjit Aulakh

(74) *Attorney, Agent, or Firm* — Shanay M. McCastle

(57) **ABSTRACT**

The present disclosure is directed to crystalline forms of morphine sulfate and pharmaceutical compositions comprising any of the crystalline forms of morphine sulfate. Also provided are processes for the preparation of crystalline forms of morphine sulfate.

9 Claims, 18 Drawing Sheets

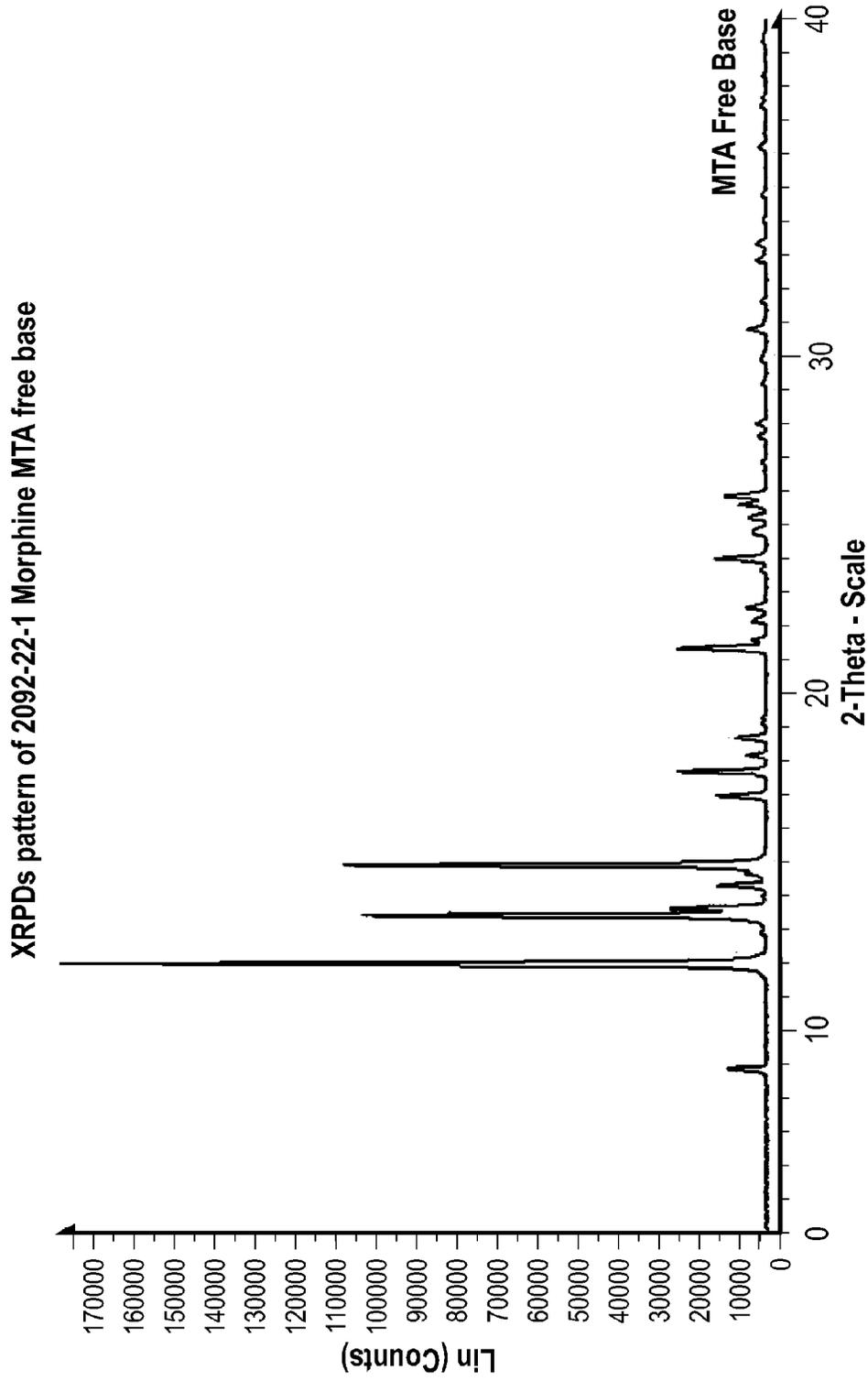


FIG. 1

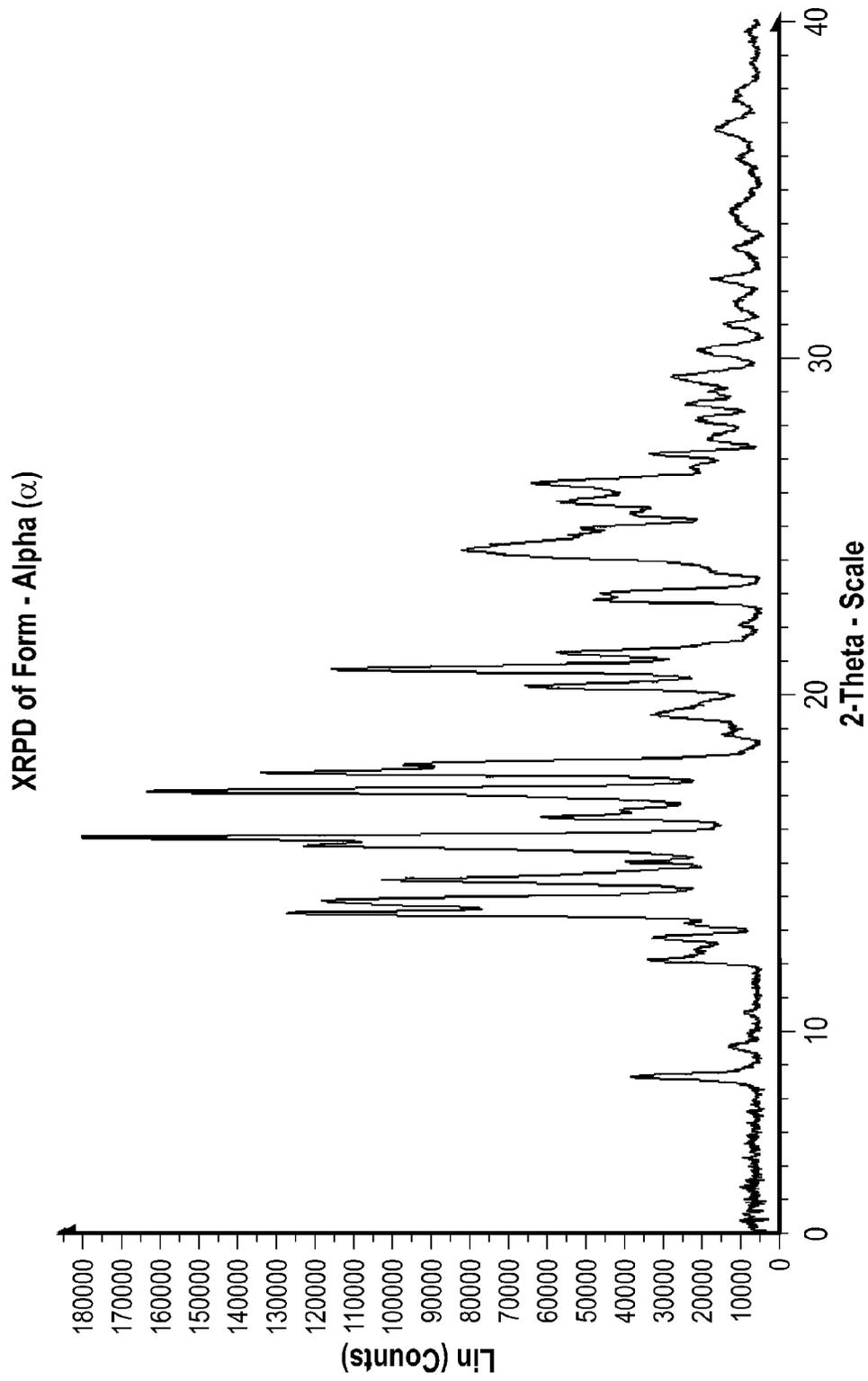


FIG. 2

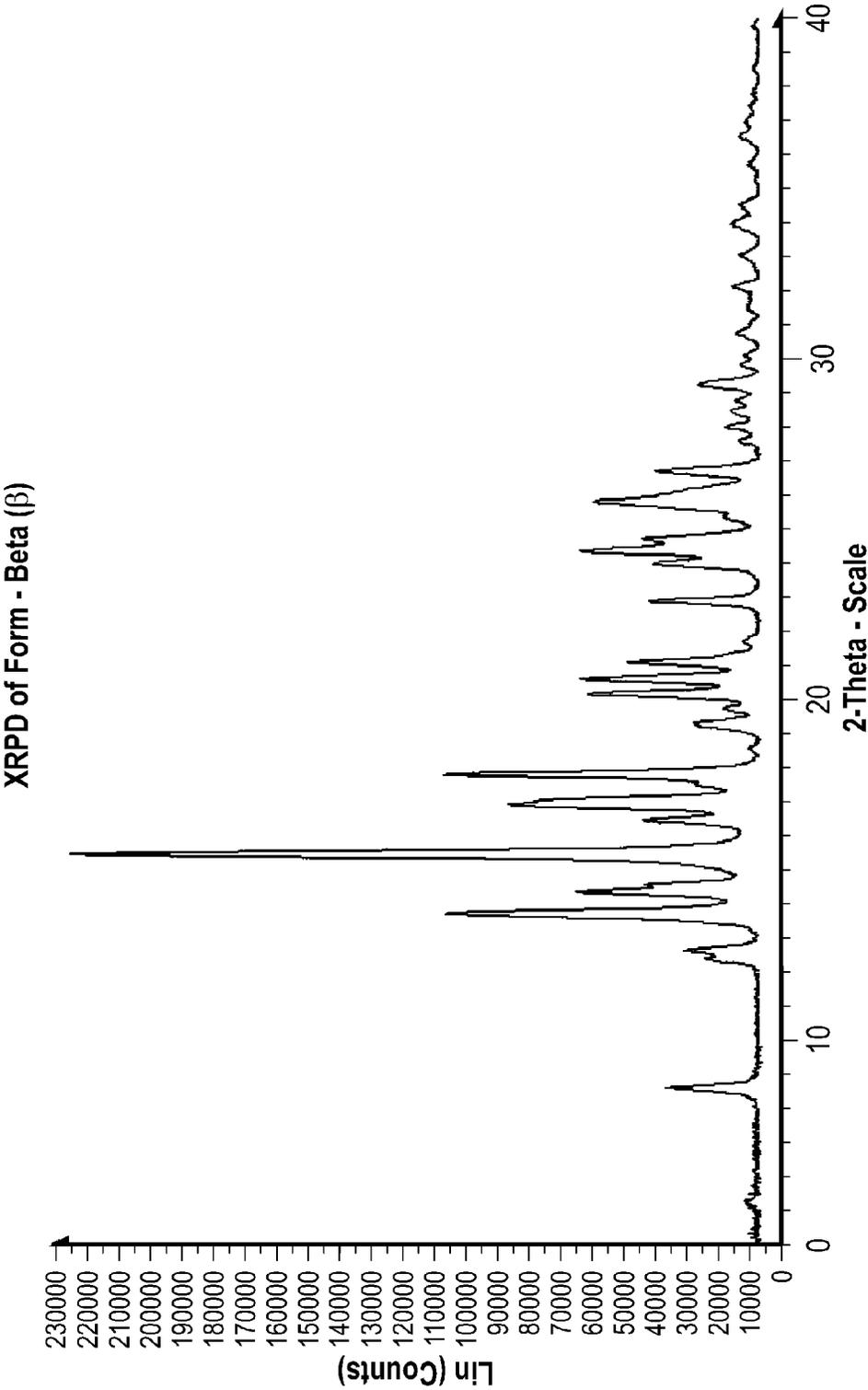


FIG. 3

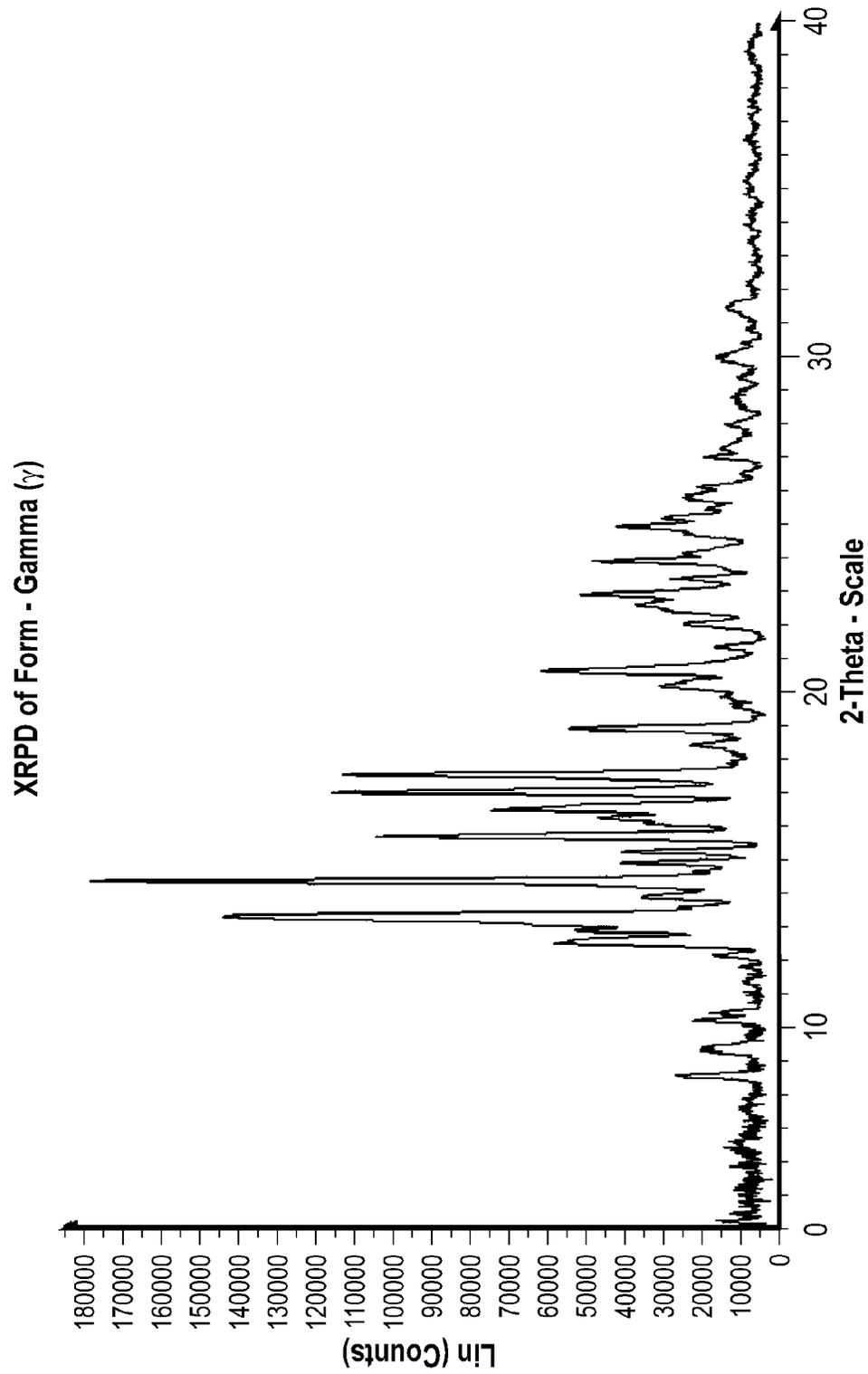


FIG. 4

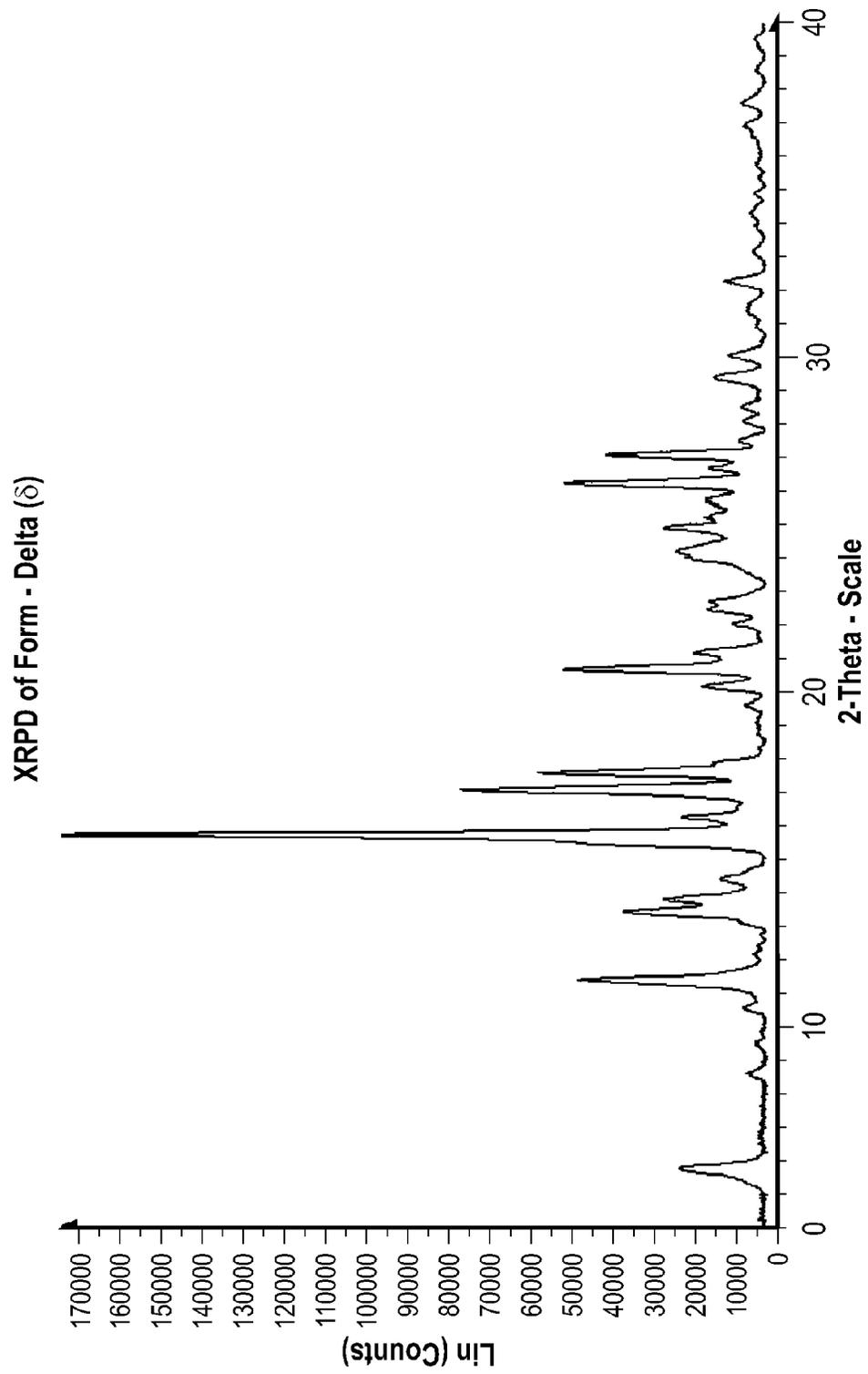


FIG. 5

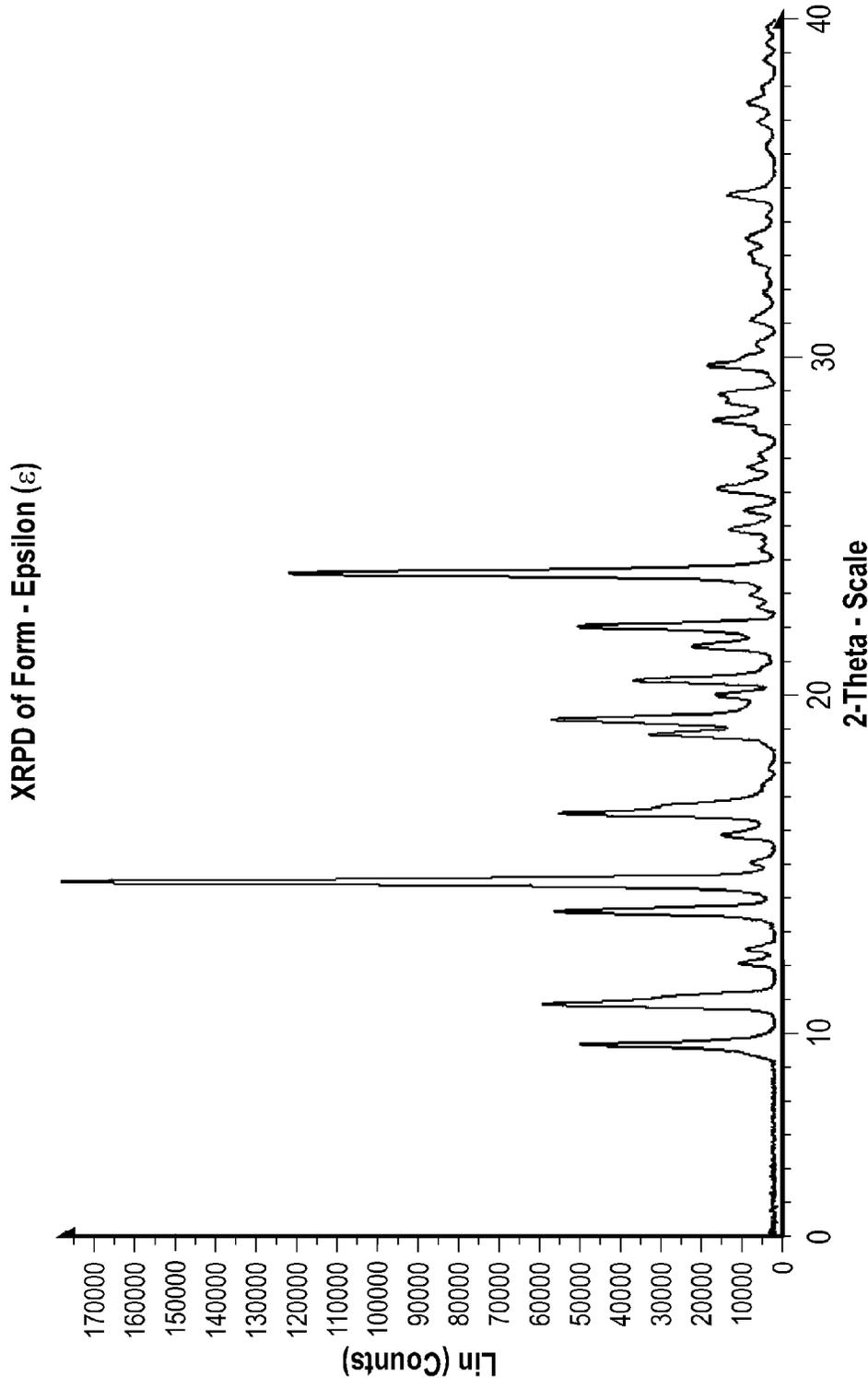


FIG. 6

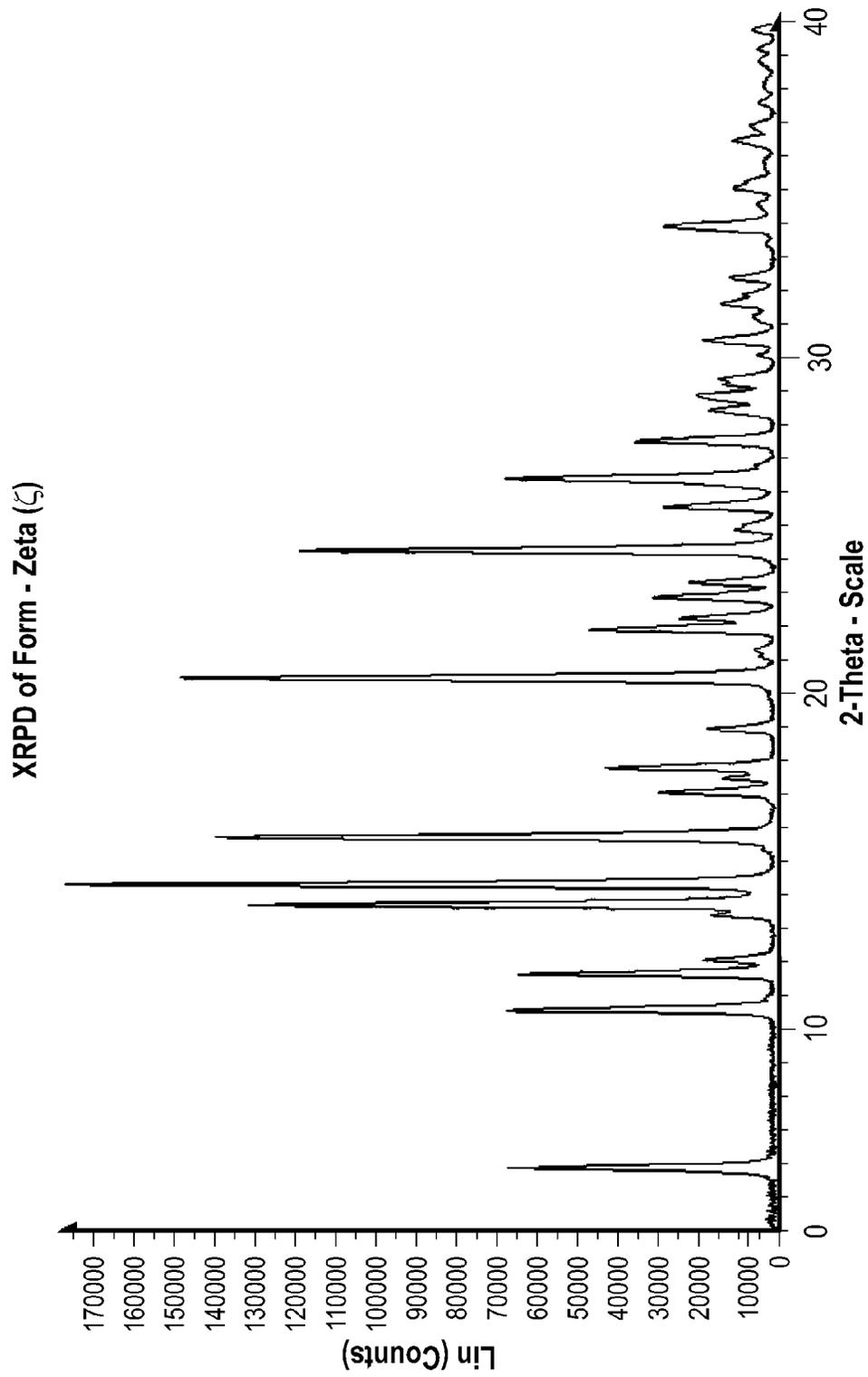


FIG. 7

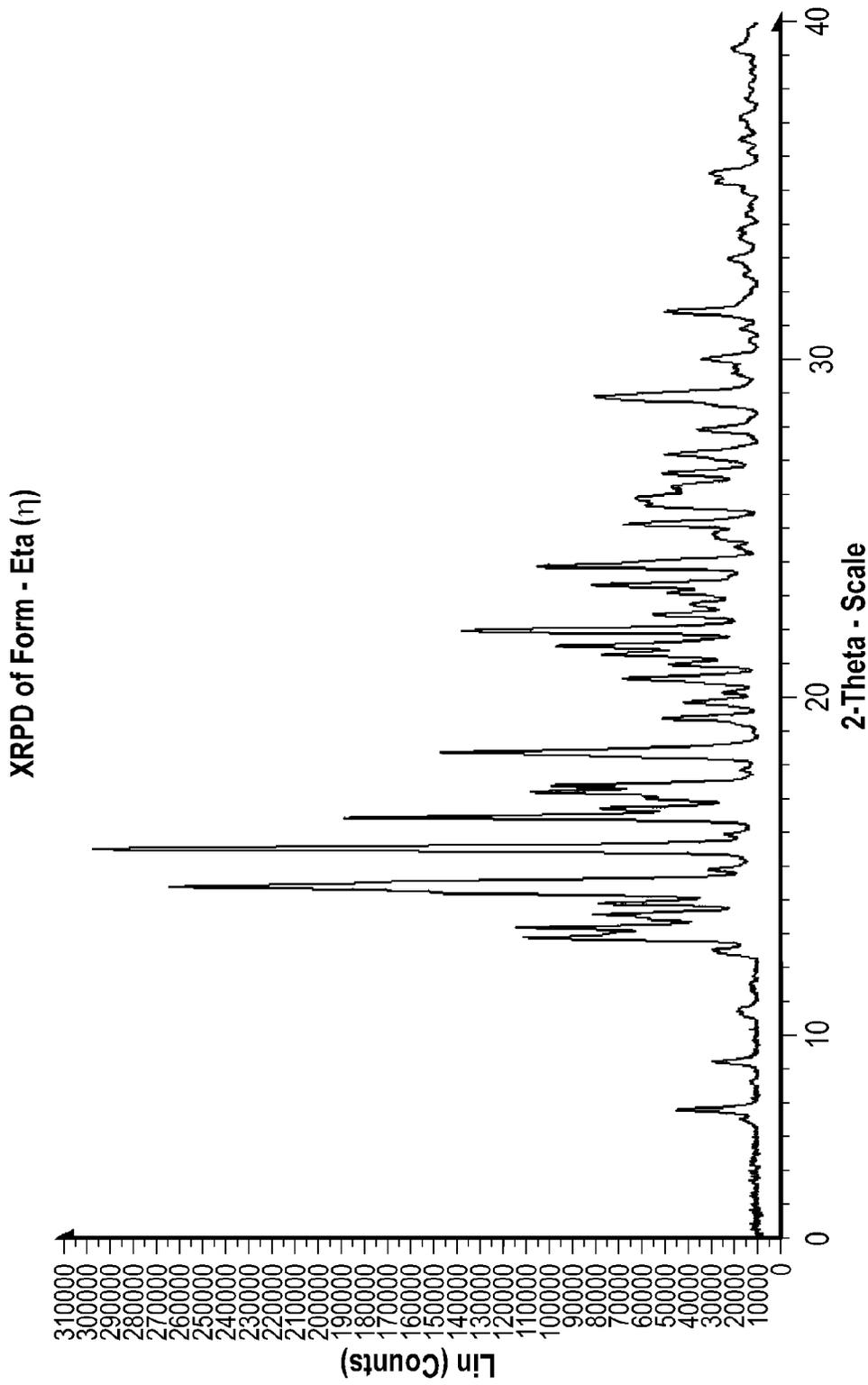


FIG. 8

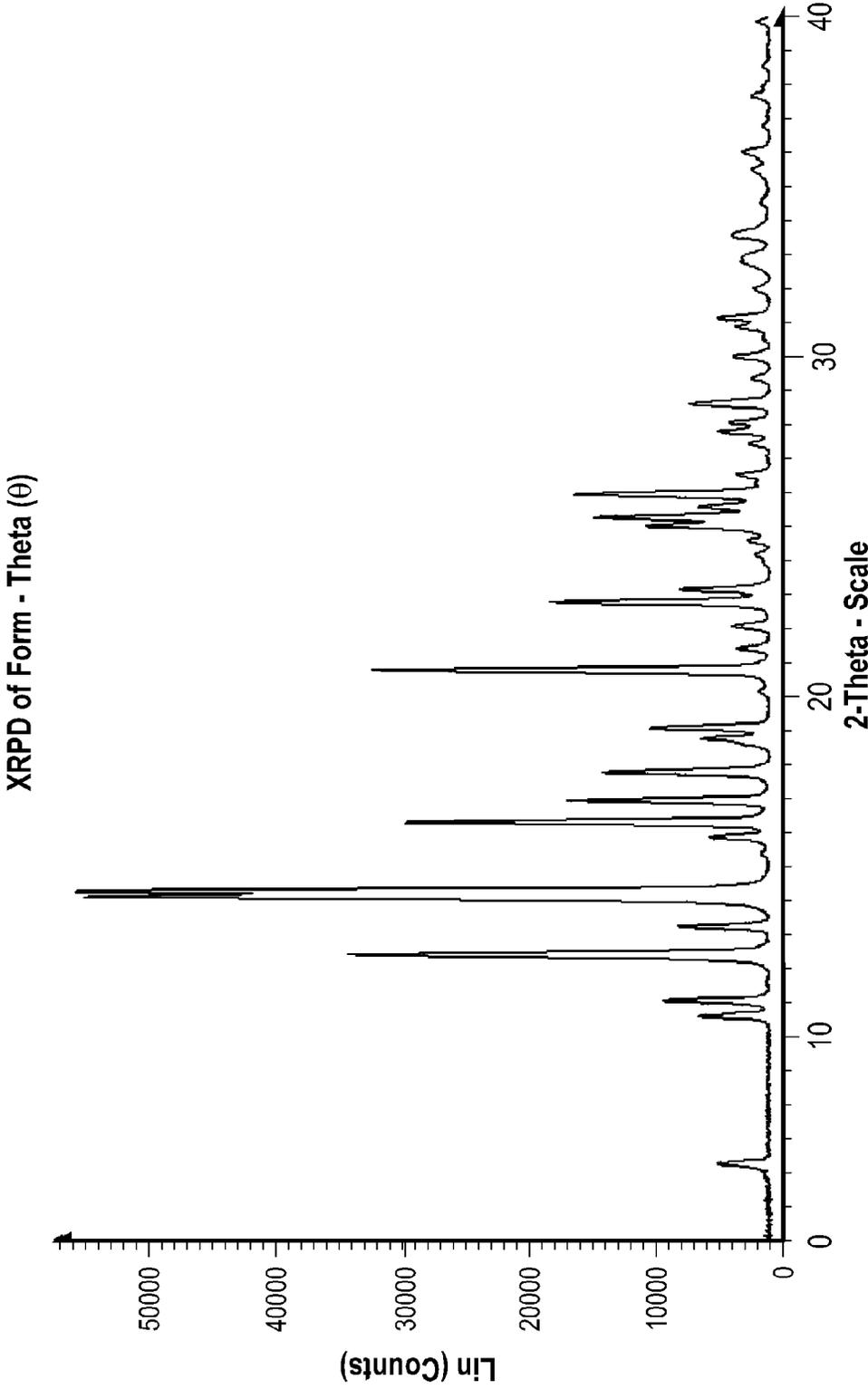


FIG. 9

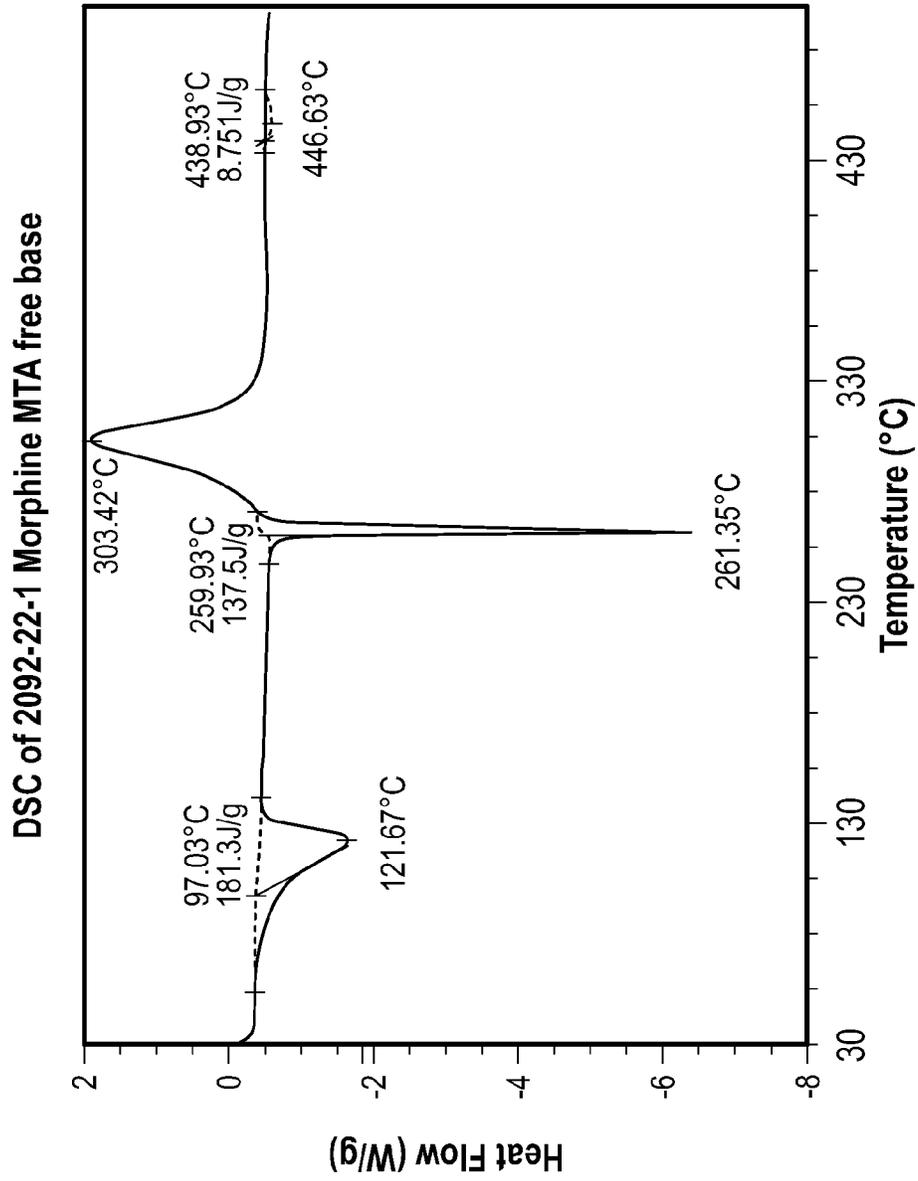


FIG. 10

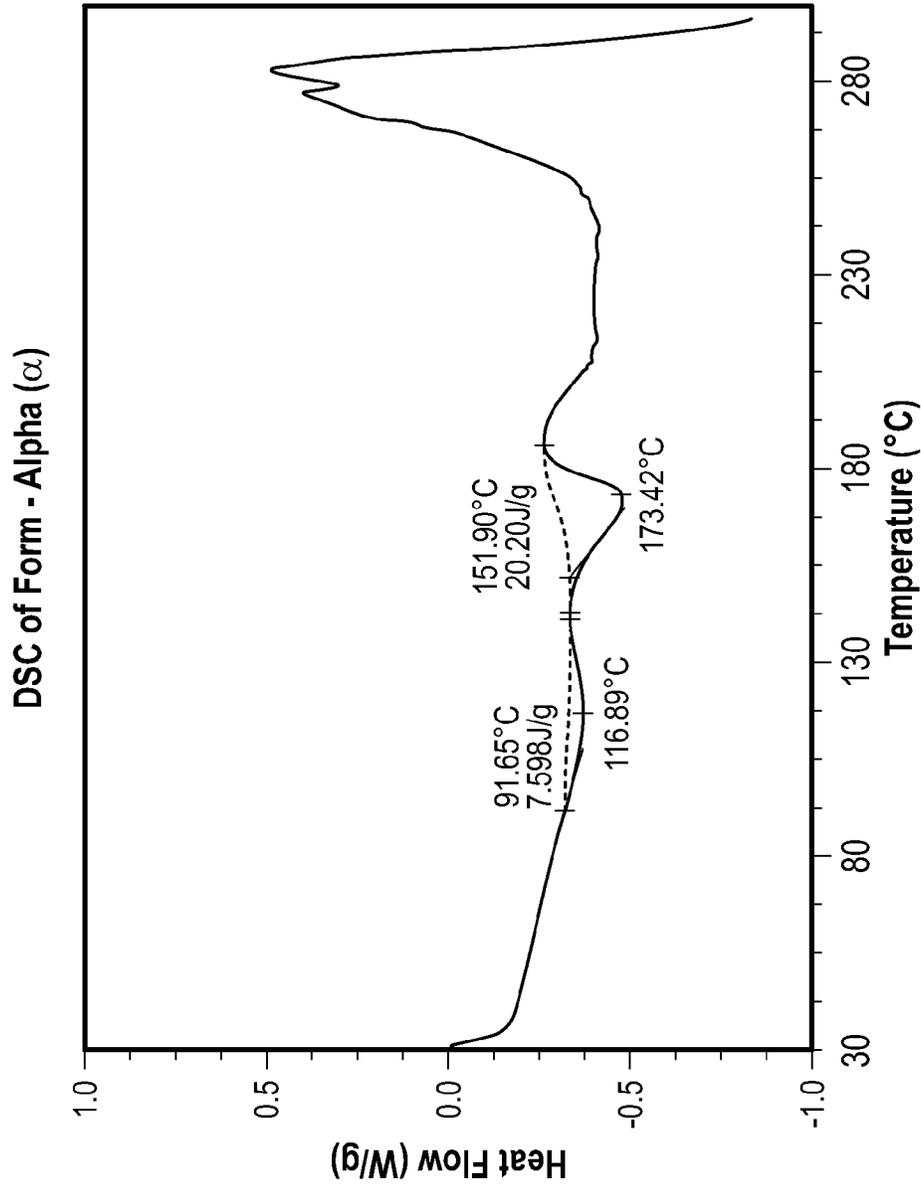


FIG. 11

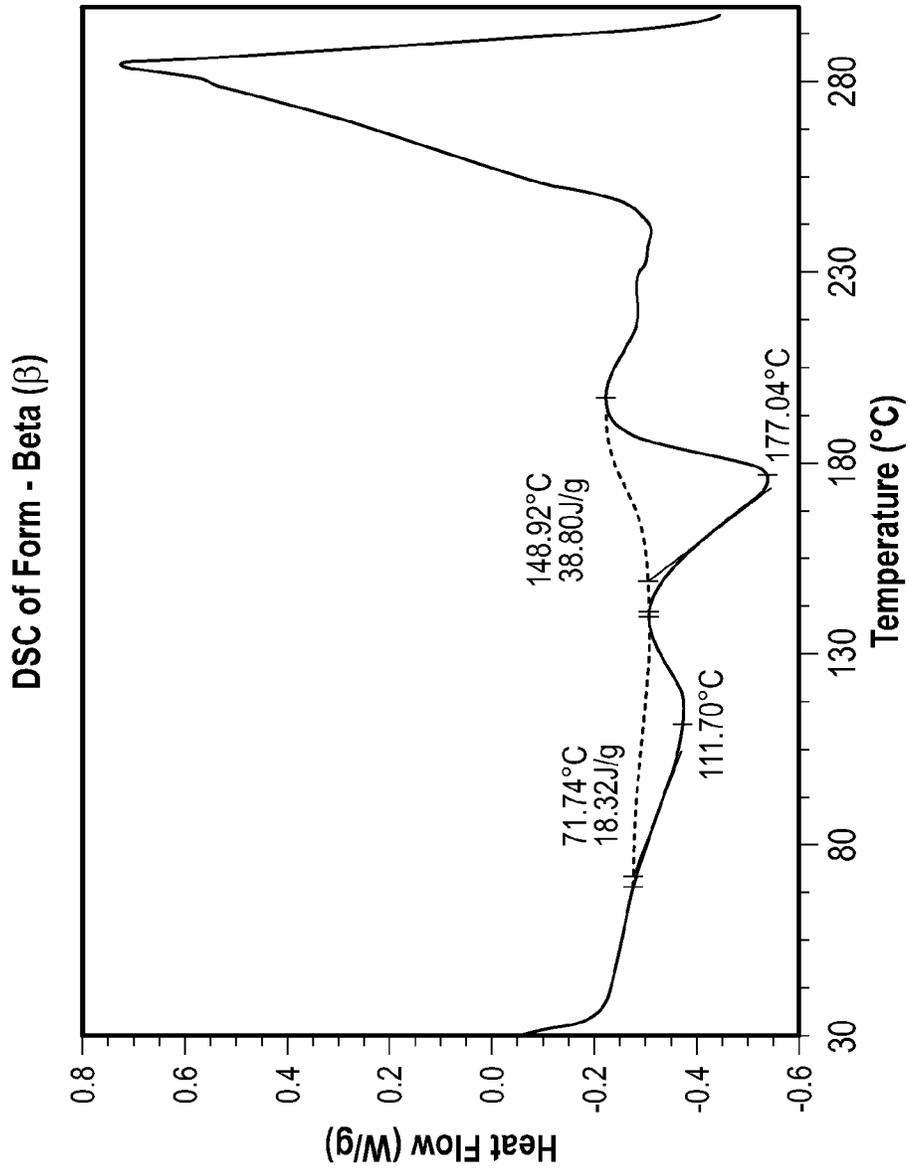


FIG. 12

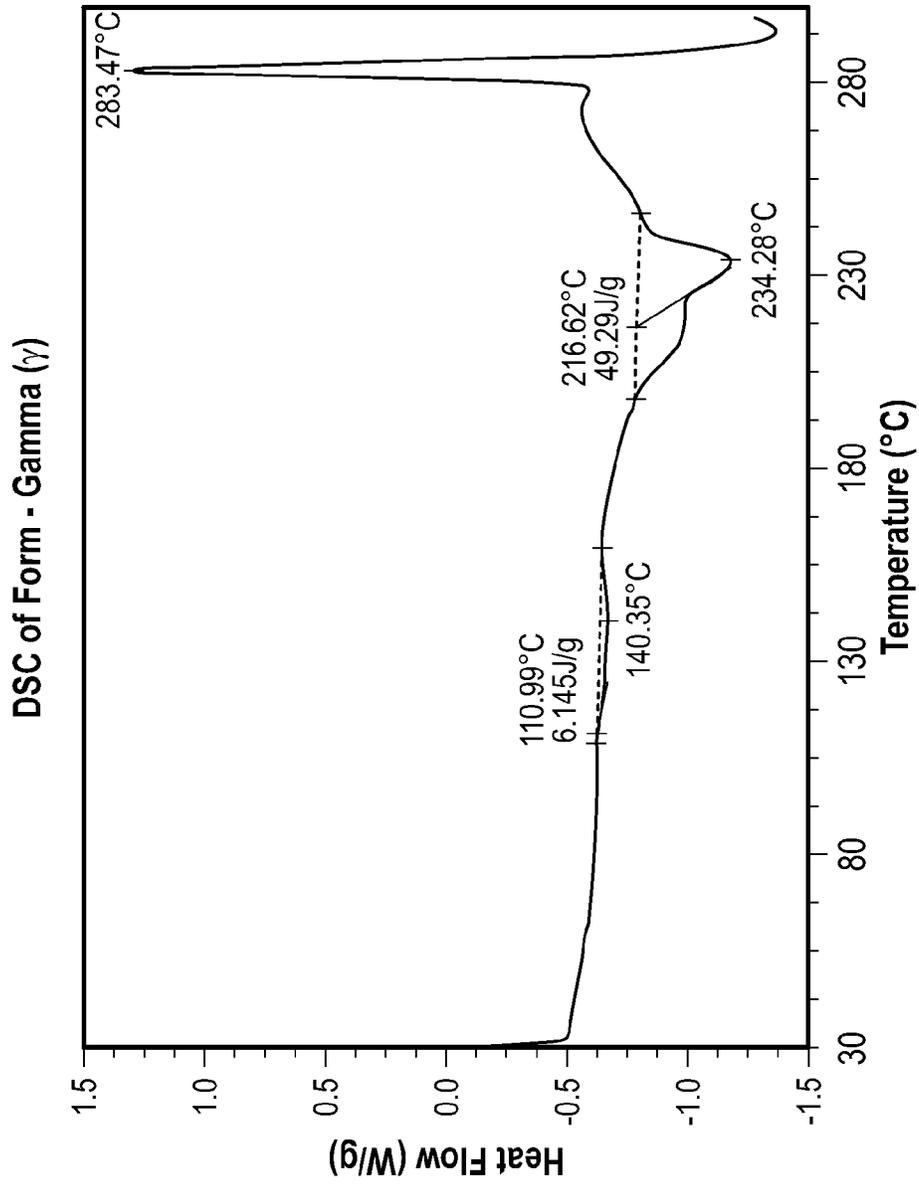


FIG. 13

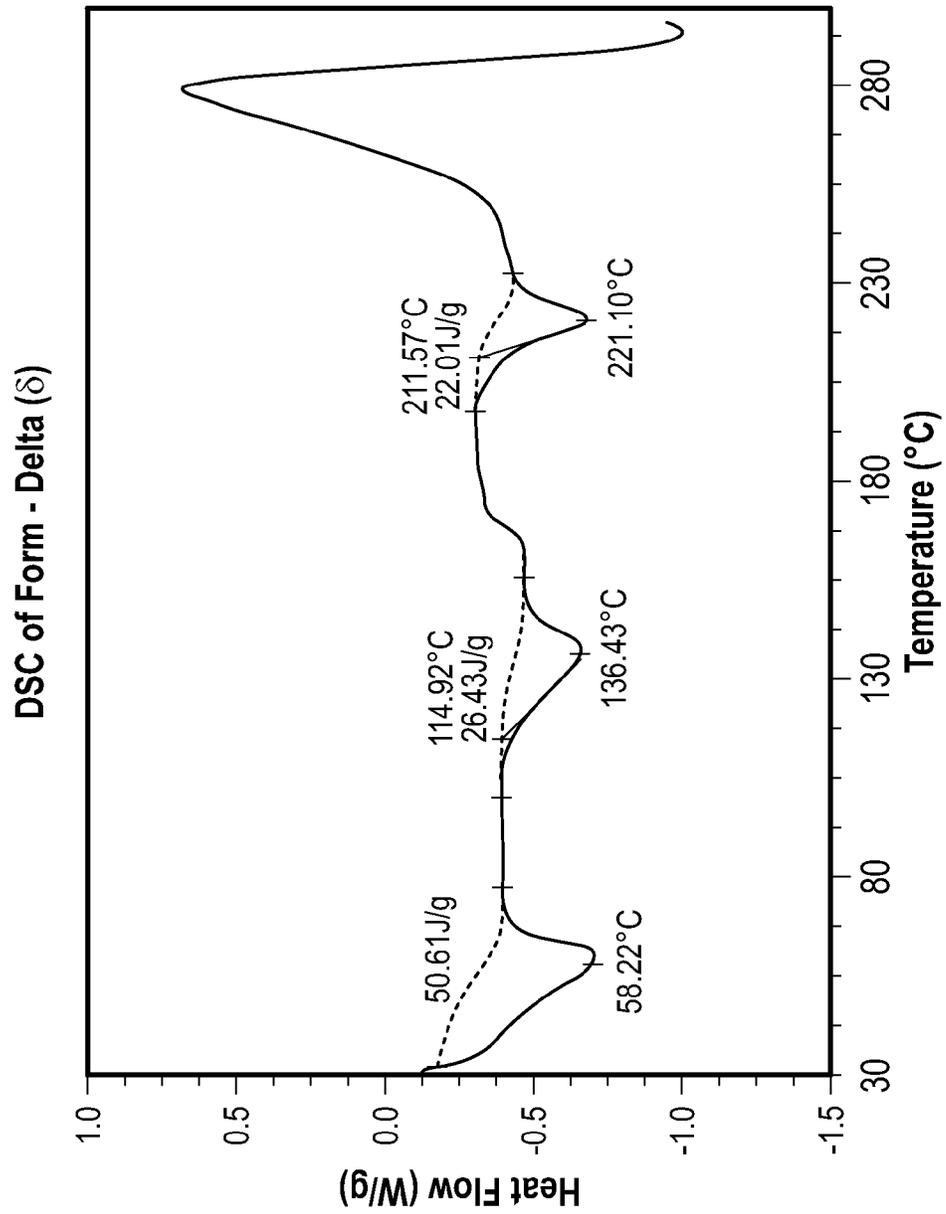


FIG. 14

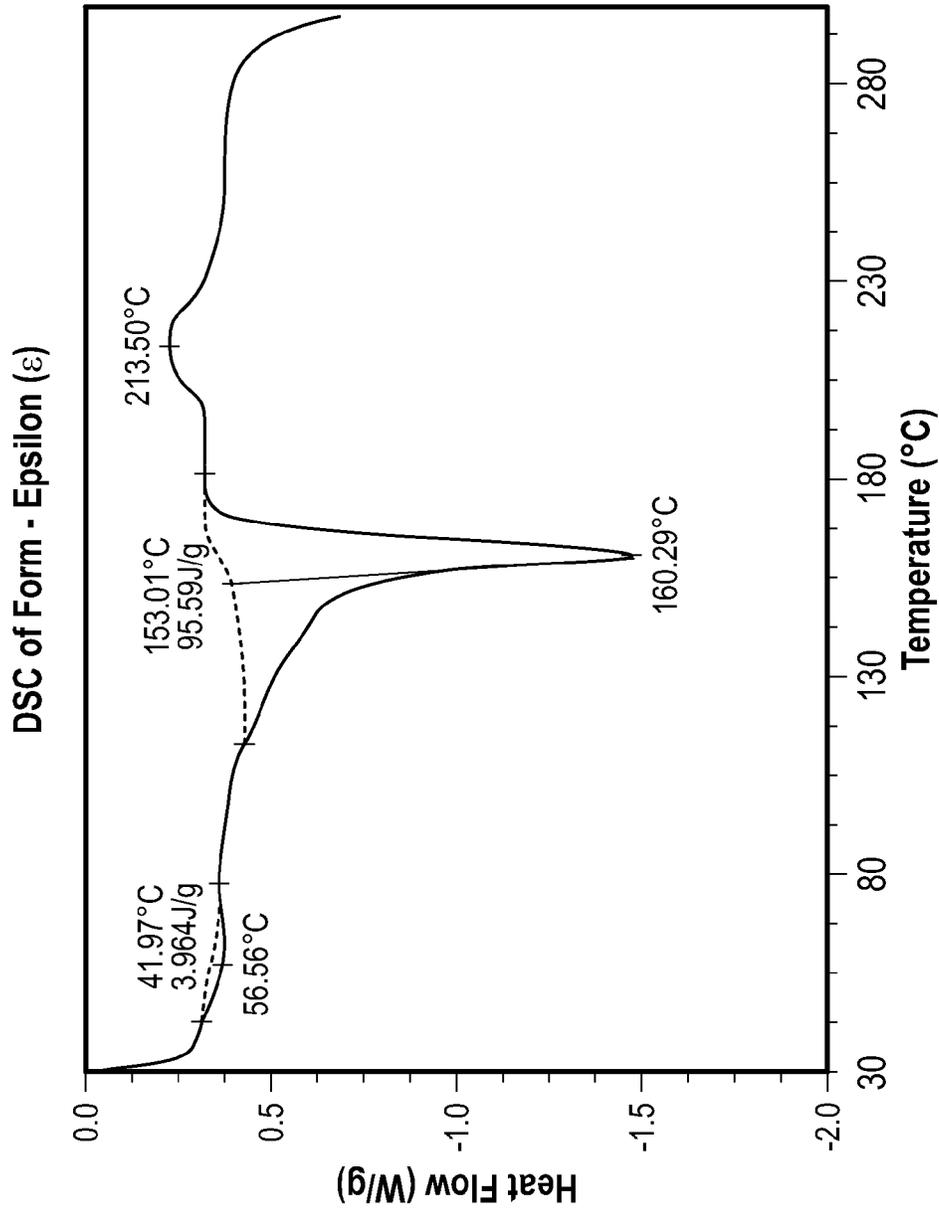


FIG. 15

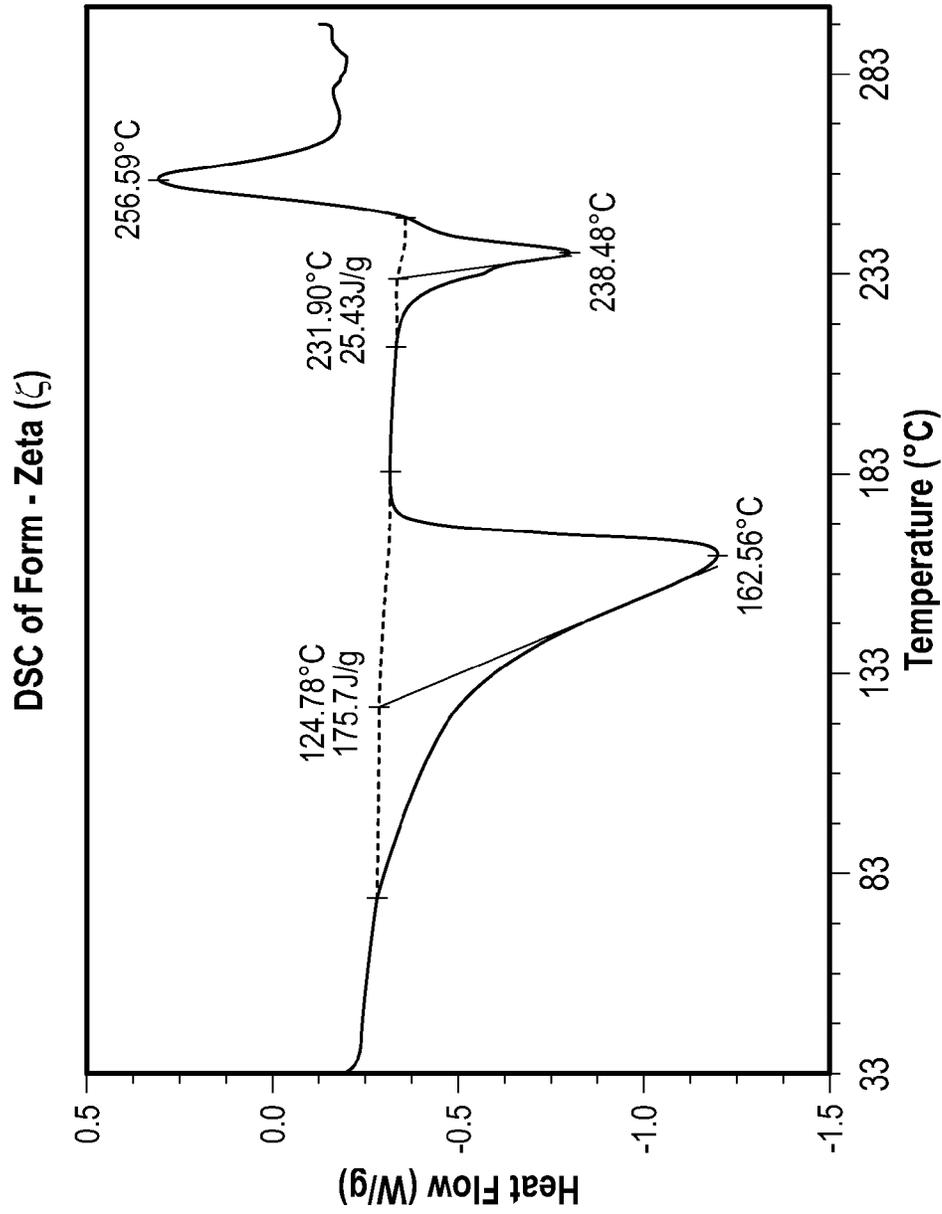


FIG. 16

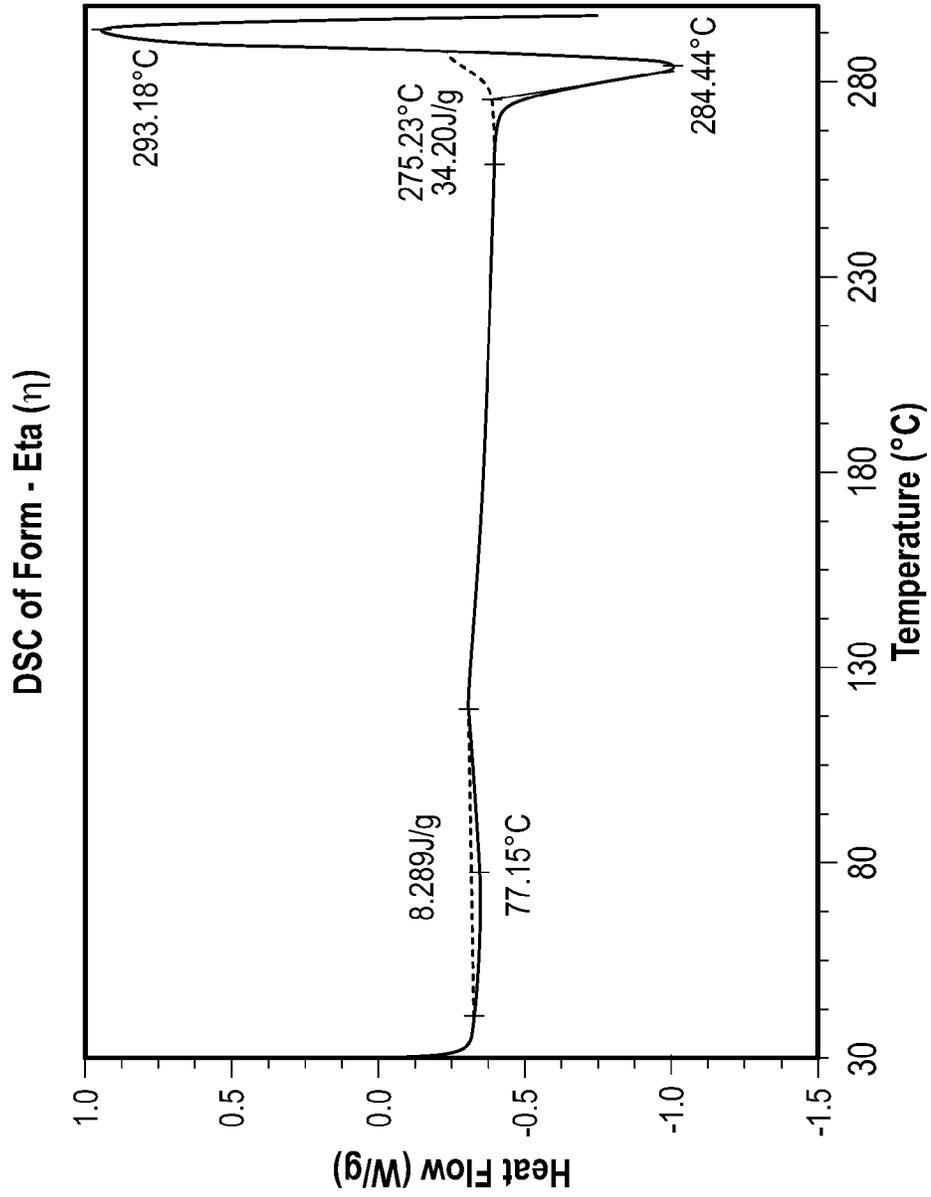


FIG. 17

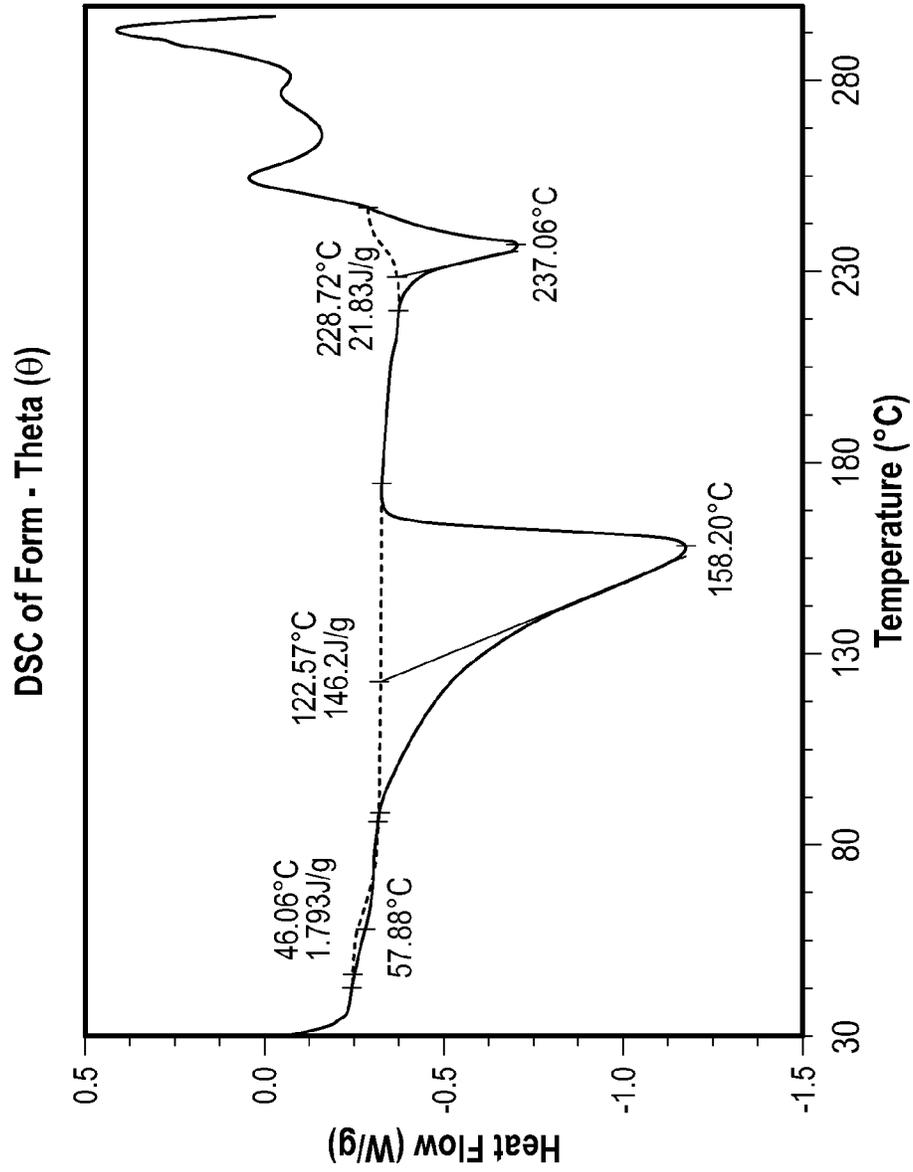


FIG. 18

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CRYSTALLINE FORMS OF MORPHINE SULFATE

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 14/670,493, filed Mar. 27, 2015, the disclosures of which are incorporated herein by reference in their entireties for all purposes.

FIELD OF THE INVENTION

The present disclosure relates to crystalline forms of morphine sulfate, and methods for making the same. The present disclosure also relates to pharmaceutical compositions containing morphine sulfate and methods for treating pain using such compositions.

BACKGROUND OF THE INVENTION

Morphine is the most abundant of at least 50 alkaloids found in opium, poppy and poppy derivatives, *Papaver somniferum*. Poppy straw is opium poppy (*Poppy somniferum*) that is harvested when fully mature and dry, minus the ripe poppy seeds. An agricultural by-product of the poppy seed harvest, the straw was a waste product before the 1930s when a chemical process became available to extract morphine from it. Poppy straw consisting mainly of the capsule became a valuable source of morphine. Today, poppy straw is a major source of many opioids and other alkaloids. It is the source of 90% of the world supply of legal morphine (i.e. for medical and scientific use).

During processing, poppy straw is pulverized and washed many times in water and/or various acids and other chemicals to produce poppy straw concentrate (PSC) or concentrated poppy straw (CPS). Once dried, the concentrate is a beige to brown colored powder and contains salts of various alkaloids. It can range from about 9 to 30 times the morphine concentration of poppy straw. Morphine is generally 8% to 17% of the dry weight of opium, although specially-designed cultivars reach 26% or produce little morphine at all. The latter varieties, including the Przemko and Norman strains of the opium poppy, are used to produce two other alkaloids, thebaine and oripavine, which are used in the manufacture of semi-synthetic opioids like oxycodone and etorphine as well as other types of drugs. At least one manufacturer, Tasmanian Alkaloids, produces both high-morphine and high-thebaine/oripavine types of CPS.

Morphine is produced most predominantly early in the life cycle of the plant and, past the optimum point for extraction, various processes in the plant produce codeine, thebaine, and in some cases low quantities of hydromorphone, dihydromorphone, dihydrocodeine, tetrahydrothebaine and hydrocodone.

Morphine, generally administered in a salt form, is a potent opiate analgesic, for the relief of moderate to severe pain, and has been approved for use for decades. It can be administered as an injectable solution, suppository, capsule, tablet or extended release product. Like other opioids, e.g. oxycodone, hydromorphone and diacetylmorphine (heroin), morphine acts directly on the central nervous system (CNS) to relieve pain. Today, morphine sulfate is sold under various trade names including Astramorph PF™, Avinza®, Depo-Dur®, Duramorph, Infumorph, Kadian®, MS-Contin®, Oramorph® SR and RMS. Kadian® is a morphine sustained-release dosage form for once or twice per day dosing.

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Kadian® is currently available in 10, 20, 30, 40, 50, 60, 80, 100 and 200 mg morphine sulfate extended release capsules.

Morphine is regarded as the opioid drug of choice in the treatment of cancer pain, for example. Side effects of morphine treatment include, for example, nausea and vomiting, constipation, sedation, confusion and loss of appetite. It has been suggested that the use of modified release morphine formulations, apart from their convenience and their ability to provide continuous analgesia, may also result in a lower incidence and severity of morphine-related side effects. Sustained-release morphine dosage forms are described in U.S. Pat. Nos. 5,202,128, 5,215,758, 5,378,474 and 5,672,360.

All references cited herein, including the morphine sulfate products associated with the above-mentioned trade names, are incorporated herein by reference in their entireties.

SUMMARY OF THE INVENTION

The present disclosure is directed to eight novel crystalline forms of morphine sulfate. These forms are identified herein as Forms α , β , γ , δ , ϵ , ζ , η and θ . The present disclosure is further directed to processes for the preparation of the crystalline forms of morphine sulfate as herein described.

Illustrative of the present disclosure is a pharmaceutical composition comprising at least one pharmaceutically acceptable excipient and any of the crystalline forms of morphine sulfate as herein described. An illustration of the present disclosure is a pharmaceutical composition made by mixing any of the crystalline forms of morphine sulfate as herein described and at least one pharmaceutically acceptable excipient. Illustrating the present disclosure is a process for making a pharmaceutical composition comprising mixing any of the crystalline forms of morphine sulfate as herein described and at least one pharmaceutically acceptable excipient.

Exemplifying the present disclosure are methods of treating pain, comprising administering to a subject in need thereof, one or more of the morphine sulfate crystalline forms or pharmaceutical compositions described above.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is an X-ray powder diffractogram of morphine free base, expressed in terms of $^{\circ} 2\theta$.

FIG. 2 is an X-ray powder diffractogram of morphine sulfate crystalline Form α , expressed in terms of $^{\circ} 2\theta$.

FIG. 3 is an X-ray powder diffractogram of morphine sulfate crystalline Form β , expressed in terms of $^{\circ} 2\theta$.

FIG. 4 is an X-ray powder diffractogram of morphine sulfate crystalline Form γ , expressed in terms of $^{\circ} 2\theta$.

FIG. 5 is an X-ray powder diffractogram of morphine sulfate crystalline Form δ , expressed in terms of $^{\circ} 2\theta$.

FIG. 6 is an X-ray powder diffractogram of morphine sulfate crystalline Form ϵ , expressed in terms of $^{\circ} 2\theta$.

FIG. 7 is an X-ray powder diffractogram of morphine sulfate crystalline Form ζ , expressed in terms of $^{\circ} 2\theta$.

FIG. 8 is an X-ray powder diffractogram of morphine sulfate crystalline Form η , expressed in terms of $^{\circ} 2\theta$.

FIG. 9 is an X-ray powder diffractogram of morphine sulfate crystalline Form θ , expressed in terms of $^{\circ} 2\theta$.

FIG. 10 is a measured differential scanning calorimetry thermogram of morphine free base.

FIG. 11 is a measured differential scanning calorimetry thermogram of morphine sulfate crystalline Form α .

FIG. 12 is a measured differential scanning calorimetry thermogram of morphine sulfate crystalline Form β .

FIG. 13 is a measured differential scanning calorimetry thermogram of morphine sulfate crystalline Form γ .

FIG. 14 is a measured differential scanning calorimetry thermogram of morphine sulfate crystalline Form δ .

FIG. 15 is a measured differential scanning calorimetry thermogram of morphine sulfate crystalline Form ϵ .

FIG. 16 is a measured differential scanning calorimetry thermogram of morphine sulfate crystalline Form ζ .

FIG. 17 is a measured differential scanning calorimetry thermogram of morphine sulfate crystalline Form η .

FIG. 18 is a measured differential scanning calorimetry thermogram of morphine sulfate crystalline Form θ .

DETAILED DESCRIPTION OF THE INVENTION

The present disclosure is directed to eight novel crystalline forms of morphine sulfate, as herein described in detail. More particularly, the present disclosure is directed to novel crystalline Forms α , β , γ , δ , ϵ , ζ , η and θ of morphine sulfate.

The present disclosure is further directed to processes for the preparation of the crystalline forms of morphine sulfate, as described in more detail in the Examples which follow herein.

The present disclosure is further directed to pharmaceutical compositions comprising one or more of the crystalline forms of morphine sulfate. The present disclosure is further directed to a method of treating pain comprising administering to a subject in need thereof, one or more of the forms of morphine sulfate.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

The term "excipient" as used herein refers to a pharmaceutically acceptable organic or inorganic carrier substance. Excipients may be natural or synthetic substances formulated alongside the active ingredient of a medication, included for the purpose of bulking-up formulations that contain potent active ingredients (thus often referred to as "bulking agents," "fillers," or "dilutents"), or to confer a therapeutic enhancement on the active ingredient in the final dosage form, such as facilitating drug absorption or solubility. Excipients can also be useful in the manufacturing process, to aid in the handling of the active substance, such as by facilitating powder flowability or non-stick properties, in addition to aiding in vitro stability such as prevention of denaturation over the expected shelf life.

The term "subject" as used herein refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment. Preferably, the subject has experienced and/or exhibited at least one symptom of the disease or disorder to be treated and/or prevented. Further, a subject may not have exhibited any symptoms of the disorder, disease or condition to be treated and/prevented, but has been deemed by a physician, clinician or other medical professional to be at risk for developing said disorder, disease or condition.

The terms "treating," "treatment" and the like as used herein shall include the management and care of a subject (preferably a mammal, more preferably a human) for the purpose of combating a disease, condition, or disorder and includes the administration of a compound of the present disclosure to prevent the onset of the symptoms or compli-

cations, alleviate the symptoms or complications, or eliminate the disease, condition, or disorder.

The crystalline forms of morphine sulfate of the present disclosure may be prepared directly or indirectly from morphine free base. Examples 1-10, which follow herein, provide embodiments of the preparation of the crystalline forms of morphine sulfate.

The crystalline forms of morphine sulfate herein described may be characterized by one or more of their characteristic physical properties including, but not limited to, X-ray powder diffraction peaks and differential scanning calorimetry.

The crystalline forms of morphine sulfate may be identified by their X-ray powder diffraction peaks/pattern. X-ray powder diffraction analysis on representative samples of the crystalline forms of morphine sulfate as herein described is performed using a Bruker D8 Advance instrument equipped with a Cu K α radiation source (1.54 $^\circ$ Angstrom), a θ -position sample holder and a LYNXEYETM Super Speed Detector. Samples are placed on zero-background, silicon plate holders.

One skilled in the art would recognize that the $^\circ 2\theta$ values and the relative intensity values are generated by performing a peak search on the measured data and the d-spacing values are calculated by the instrument from the $^\circ 2\theta$ values using Bragg's equation. One skilled in the art would further recognize that the relative intensity for the measured peaks may vary as a result of sample preparation, orientation and instrument used, for example. A variation of about ± 0.2 is not atypical in obtainable 2θ values.

Morphine sulfate Form α is a unique crystalline phase. Morphine sulfate Form α may be characterized as a white to off-white powder. Morphine sulfate Form α is further characterized by its X-ray powder diffraction pattern peaks and/or d-spacing values, as listed in Table 1 below. FIG. 2 is a representative X-ray powder diffractogram for a representative sample of morphine sulfate Form α made according to Examples 3 and 4.

TABLE 1

XRPD peak list of Form α			
2θ	d spacing, A $^\circ$	Count	%
7.54	11.721	7785	4.3
8.61	10.268	38031	21.1
9.49	9.312	12778	7.1
9.85	8.973	7574	4.2
10.49	8.429	8583	4.8
12.07	7.328	33865	18.7
12.72	6.954	32689	18.1
13.14	6.735	24265	13.4
13.45	6.576	127441	70.6
13.81	6.405	116666	64.6
14.45	6.125	102448	56.7
14.98	5.908	39629	21.9
15.48	5.721	123015	68.1
15.71	5.635	180619	100
16.32	5.429	61348	34
16.53	5.360	41019	22.7
17.08	5.187	163643	90.6
17.63	5.026	134116	74.3
17.86	4.964	97291	53.9
18.78	4.721	13223	7.3
19.36	4.581	32796	18.2
19.69	4.506	20822	11.5
20.20	4.394	65519	36.3
20.71	4.286	115491	63.9
21.19	4.190	57204	31.7
22.03	4.032	10157	5.6
22.94	3.874	46005	25.5

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TABLE 1-continued

XRPD peak list of Form α			
2 θ	d spacing, A $^\circ$	Count	%
23.63	3.762	18021	10
24.24	3.669	82081	45.4
24.88	3.575	50940	28.2
25.32	3.514	38533	21.3
25.69	3.466	57300	31.7
26.22	3.396	63972	35.4
26.70	3.336	23001	12.7
27.09	3.289	33408	18.5
27.55	3.235	18065	10
28.12	3.171	21428	11.9
28.59	3.120	23902	13.2
28.94	3.083	17979	10
29.37	3.039	27704	15.3
30.17	2.960	21079	11.7
30.93	2.889	14141	7.8
31.54	2.834	11195	6.2
32.27	2.772	17448	9.7
33.212	2.69534	11463	6.3
33.974	2.63664	10917	6
34.293	2.61282	12547	6.9
35.837	2.50371	10904	6
36.722	2.4454	16439	9.1
37.636	2.38808	11620	6.4
37.839	2.37569	11178	6.2
39.62	2.27295	7555	4.2

Morphine sulfate Form β is a unique crystalline phase. Morphine sulfate Form β may be characterized as a white to off-white powder. Morphine sulfate Form β is further characterized by its X-ray powder diffraction pattern peaks and/or d-spacing values, as listed in Table 2 below. FIG. 3 is a representative X-ray powder diffractogram for a representative sample of morphine sulfate Form β made according to Example 5.

TABLE 2

XRPD peak list of Form β			
2 θ	d spacing, A $^\circ$	Count	%
5.21	16.962	9073	5
8.56	10.322	26160	14.5
12.36	7.156	18702	10.4
12.60	7.020	23369	12.9
13.68	6.468	80427	44.5
14.32	6.178	49082	27.2
14.52	6.094	33095	18.3
15.43	5.738	180661	100
16.42	5.394	35816	19.8
16.89	5.246	68594	38
17.78	4.984	82044	45.4
18.55	4.779	8643	4.8
19.26	4.605	22015	12.2
19.72	4.499	15094	8.4
20.14	4.406	49433	27.4
20.58	4.313	50985	28.2
21.08	4.212	37666	20.8
21.67	4.097	10205	5.6
22.87	3.886	31679	17.5
23.98	3.709	31482	17.4
24.34	3.653	49142	27.2
24.69	3.603	35649	19.7
25.34	3.512	14993	8.3
25.78	3.453	48874	27.1
26.13	3.407	26087	14.4
26.68	3.339	33491	18.5
27.58	3.232	11169	6.2
27.99	3.185	13749	7.6
28.43	3.136	12380	6.9
28.75	3.102	11857	6.6
29.25	3.051	21413	11.9
29.81	2.995	10374	5.7

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TABLE 2-continued

XRPD peak list of Form β			
2 θ	d spacing, A $^\circ$	Count	%
30.75	2.906	11393	6.3
31.50	2.837	8816	4.9
32.10	2.786	12678	7
33.02	2.710	10467	5.8
33.94	2.639	12603	7
34.50	2.598	10964	6.1
35.69	2.513	8555	4.7
36.56	2.456	10659	5.9

Morphine sulfate Form γ is a unique crystalline phase. Morphine sulfate Form γ may be characterized as a white to off-white powder. Morphine sulfate Form γ is further characterized by its X-ray powder diffraction pattern peaks and/or d-spacing values, as listed in Table 3 below. FIG. 4 is a representative X-ray powder diffractogram for a representative sample of morphine sulfate Form γ made according to Example 6.

TABLE 3

XRPD peak list of Form γ			
2 θ	d spacing, A $^\circ$	Count	%
7.453	11.852	14058	7.6
8.455	10.450	30831	16.6
9.269	9.534	24458	13.2
10.115	8.738	26802	14.4
10.333	8.554	22449	12.1
11.274	7.842	13683	7.4
11.716	7.547	14746	7.9
12.049	7.340	21602	11.6
12.457	7.100	63642	34.3
12.804	6.908	58128	31.3
13.214	6.695	150759	81.2
13.811	6.407	40814	22
14.284	6.195	185710	100
14.826	5.970	46595	25.1
15.176	5.834	46458	25
15.627	5.666	110758	59.6
16.174	5.476	52472	28.3
16.445	5.386	80017	43.1
16.95	5.227	122648	66
17.467	5.073	119559	64.4
18.363	4.828	28359	15.3
18.852	4.703	59796	32.2
19.542	4.539	16054	8.6
20.129	4.408	36101	19.4
20.577	4.313	67254	36.2
21.291	4.170	21516	11.6
21.989	4.039	29706	16
22.549	3.940	42588	22.9
22.869	3.885	57195	30.8
23.329	3.810	33391	18
23.871	3.725	53918	29
24.101	3.690	30277	16.3
24.68	3.604	29904	16.1
24.903	3.573	47681	25.7
25.157	3.537	35556	19.1
25.758	3.456	30234	16.3
26.09	3.413	26587	14.3
26.474	3.364	15218	8.2
26.992	3.301	24641	13.3
27.243	3.271	19820	10.7
27.944	3.190	18586	10
28.632	3.115	15926	8.6
29.37	3.039	15433	8.3
29.953	2.981	20227	10.9
30.801	2.901	13006	7
31.443	2.843	18739	10.1

Morphine sulfate Form δ is a unique crystalline phase. Morphine sulfate Form δ may be characterized as a white to

off-white powder. Morphine sulfate Form δ is further characterized by its X-ray powder diffraction pattern peaks and/or d-spacing values, as listed in Table 4 below. FIG. 5 is a representative X-ray powder diffractogram for a representative sample of morphine sulfate Form δ made according to Example 7.

TABLE 4

XRPD peak list of Form δ			
2θ	d spacing, A $^\circ$	Count	%
5.70	15.486	23544	13.3
8.54	10.344	7313	4.1
9.43	9.368	5049	2.9
10.50	8.416	8086	4.6
11.34	7.799	48561	27.5
13.37	6.615	37282	21.1
13.76	6.432	27356	15.5
14.37	6.159	13851	7.8
15.39	5.754	44927	25.4
15.68	5.646	176656	100
16.20	5.466	23125	13.1
17.03	5.203	77012	43.6
17.54	5.051	58036	32.9
17.87	4.961	14950	8.5
19.55	4.537	7832	4.4
20.14	4.406	18108	10.3
20.64	4.299	52029	29.5
21.15	4.198	20217	11.4
21.99	4.03875	10728	6.1
22.427	3.96113	16914	9.6
22.66	3.92087	16607	9.4
24.001	3.70482	22324	12.6
24.169	3.6794	24531	13.9
24.873	3.57683	27399	15.5
25.184	3.53337	17641	10
25.71	3.46233	17253	9.8
26.202	3.39833	51837	29.3
26.659	3.34116	16594	9.4
27.052	3.2935	41688	23.6
27.477	3.24353	9229	5.2
28.06	3.17744	8234	4.7
28.488	3.13069	8906	5
29.37	3.03856	15075	8.5
30.03	2.97327	11893	6.7
31.512	2.83673	6770	3.8
32.238	2.77452	12699	7.2
33.137	2.70129	5857	3.3
34.866	2.57114	5473	3.1
35.732	2.51081	5019	2.8
36.913	2.43317	7795	4.4
37.581	2.39145	8745	5
38.562	2.33282	5063	2.9
39.5	2.27953	5249	3

Morphine sulfate Form ϵ is a unique crystalline phase. Morphine sulfate Form ϵ may be characterized as a white to off-white powder. Morphine sulfate Form ϵ is further characterized by its X-ray powder diffraction pattern peaks and/or d-spacing values, as listed in Table 5 below. FIG. 6 is a representative X-ray powder diffractogram for a representative sample of morphine sulfate Form ϵ made according to Example 8.

TABLE 5

XRPD peak list of Form ϵ			
2θ	d spacing, A $^\circ$	Count	%
9.59	9.216	49596	27.5
10.80	8.189	58820	32.6
11.03	8.012	28976	16
12.01	7.362	10490	5.8
12.41	7.125	8694	4.8

TABLE 5-continued

XRPD peak list of Form ϵ			
2θ	d spacing, A $^\circ$	Count	%
13.54	6.535	56197	31.1
14.40	6.145	180610	100
14.98	5.911	7730	4.3
15.79	5.608	15043	8.3
16.44	5.389	54987	30.4
16.67	5.313	30704	17
17.22	5.144	4957	2.7
17.78	4.984	3188	1.8
18.77	4.723	32612	18.1
19.20	4.620	56708	31.4
19.92	4.453	16250	9
20.38	4.355	36651	20.3
21.42	4.145	21869	12.1
22.01	4.036	50499	28
22.59	3.934	5792	3.2
22.94	3.874	7766	4.3
23.58	3.770	121785	67.4
24.29	3.661	5575	3.1
24.87	3.577	13138	7.3
25.44	3.498	9570	5.3
26.08	3.414	16116	8.9
26.73	3.333	8477	4.7
27.10	3.288	5473	3
27.78	3.209	7022	3.9
28.09	3.174	17147	9.5
28.66	3.113	13869	7.7
28.87	3.090	15599	8.6
29.73	3.003	18568	10.3
30.35	2.942	6191	3.4
31.08	2.876	7841	4.3
31.87	2.806	4392	2.4
32.82	2.726	6976	3.9
33.03	2.710	8059	4.5
33.48	2.674	8999	5
34.77	2.578	13351	7.4
36.18	2.481	3929	2.2
36.93	2.432	5783	3.2
37.50	2.396	8307	4.6
37.93	2.370	4888	2.7
38.76	2.321	4425	2.4
39.26	2.293	3838	2.1
39.72	2.267	3764	2.1

Morphine sulfate Form ζ is a unique crystalline phase. Morphine sulfate Form ζ may be characterized as a white to off-white powder. Morphine sulfate Form ζ is further characterized by its X-ray powder diffraction pattern peaks and/or d-spacing values, as listed in Table 6 below. FIG. 7 is a representative X-ray powder diffractogram for a representative sample of morphine sulfate Form ζ made according to Example 9.

TABLE 6

XRPD peak list of Form ζ			
2θ	d spacing, A $^\circ$	Count	%
5.83	15.145	67066	37.9
10.53	8.397	67455	38.1
11.61	7.613	64699	36.6
12.03	7.353	18553	10.5
13.37	6.617	16740	9.5
13.67	6.475	131887	74.5
14.28	6.198	177010	100
15.68	5.646	139905	79
17.03	5.203	29597	16.7
17.45	5.078	13720	7.8
17.76	4.989	42869	24.2
18.93	4.685	17523	9.9
20.44	4.342	148314	83.8
21.28	4.173	5956	3.4
21.89	4.056	47000	26.6

TABLE 6-continued

XRPD peak list of Form ζ			
2θ	d spacing, A°	Count	%
22.24	3.995	24366	13.8
22.86	3.888	31247	17.7
23.30	3.815	22223	12.6
24.24	3.668	118902	67.2
24.89	3.575	10814	6.1
25.56	3.482	28441	16.1
26.39	3.374	67762	38.3
26.81	3.323	5745	3.2
27.52	3.239	35467	20
28.44	3.136	17251	9.7
28.87	3.091	20379	11.5
29.26	3.049	12317	7
30.08	2.968	5088	2.9
30.52	2.927	18570	10.5
31.22	2.862	6028	3.4
31.62	2.827	14302	8.1
31.88	2.805	8467	4.8
32.39	2.762	12007	6.8
33.42	2.679	3102	1.8
33.93	2.640	28295	16
34.59	2.591	5340	3
35.08	2.556	10972	6.2
36.49	2.460	11523	6.5
36.92	2.433	7022	4
37.62	2.389	4998	2.8
38.25	2.351	3796	2.1
38.89	2.314	5009	2.8
39.24	2.294	5205	2.9
39.80	2.263	6548	3.7

Morphine sulfate Form η is a unique crystalline phase. Morphine sulfate Form η may be characterized as a white to off-white powder. Morphine sulfate Form η is further characterized by its X-ray powder diffraction pattern peaks and/or d-spacing values, as listed in Table 7 below. FIG. 8 is a representative X-ray powder diffractogram for a representative sample of morphine sulfate Form η made according to Example 10.

TABLE 7

XRPD peak list of Form η			
2θ	d spacing, A°	Count	%
7.75	11.405	4463	15
9.16	9.643	2920	9.8
10.71	8.258	1812	6.1
12.46	7.100	2817	9.5
12.87	6.875	11111	37.3
13.15	6.727	11390	38.3
13.52	6.545	8090	27.2
13.88	6.374	7809	26.2
14.36	6.162	26492	89
14.87	5.952	3086	10.4
15.49	5.717	29771	100
16.42	5.394	18857	63.3
16.68	5.311	7777	26.1
17.19	5.156	10816	36.3
17.36	5.103	9882	33.2
18.33	4.835	14720	49.4
19.37	4.580	5087	17.1
19.83	4.473	4094	13.8
20.14	4.405	2502	8.4
20.54	4.320	6772	22.7
20.97	4.234	4808	16.2
21.27	4.175	7703	25.9
21.51	4.128	9621	32.3
21.96	4.045	13770	46.3
22.44	3.959	5453	18.3
22.73	3.909	3857	13
23.09	3.848	4832	16.2
23.31	3.813	8138	27.3

TABLE 7-continued

XRPD peak list of Form η			
2θ	d spacing, A°	Count	%
23.88	3.723	10490	35.2
24.81	3.585	2936	9.9
25.12	3.542	6737	22.6
25.70	3.463	5827	19.6
25.88	3.440	6250	21
26.21	3.397	4614	15.5
26.64	3.344	5066	17
27.20	3.276	4950	16.6
27.93	3.192	3596	12.1
28.89	3.088	7990	26.8
30.03	2.974	3414	11.5
31.43	2.844	4953	16.6
32.98	2.713	2238	7.5
35.52	2.525	3025	10.2
39.21	2.296	2068	6.9

Morphine sulfate Form θ is a unique crystalline phase. Morphine sulfate Form θ may be characterized as a white to off-white powder. Morphine sulfate Form θ is further characterized by its X-ray powder diffraction pattern peaks and/or d-spacing values, as listed in Table 8 below. FIG. 9 is a representative X-ray powder diffractogram for a representative sample of morphine sulfate Form θ made according to Example 11.

TABLE 8

XRPD peak list of Form θ			
2θ	d spacing, A°	Count	%
4.17	4.172	44.5	0.1
4.27	4.269	36.4	0.1
6.20	6.197	4012	7.3
10.56	10.556	5607	10.2
11.00	11.001	8375	15.3
12.36	12.359	33350	60.8
13.18	13.180	7125	13
14.05	14.050	54408	99.2
14.22	14.215	54834	100
15.33	15.328	599	1.1
15.81	15.812	4672	8.5
16.26	16.255	28665	52.3
16.90	16.897	15956	29.1
17.73	17.726	13145	24
18.72	18.716	5306	9.7
19.03	19.026	9348	17
20.12	20.118	828	1.5
20.73	20.733	31446	57.3
21.38	21.376	2555	4.7
22.04	22.037	2930	5.3
22.74	22.742	17287	31.5
23.11	23.109	6983	12.7
24.14	24.138	1040	1.9
24.54	24.538	1670	3
24.99	24.990	9728	17.7
25.25	25.247	13894	25.3
25.56	25.561	5572	10.2
25.92	25.923	15440	28.2
26.50	26.496	2590	4.7
27.40	27.402	1552	2.8
27.75	27.752	4031	7.4
28.03	28.025	3130	5.7
28.59	28.592	6237	11.4
29.34	29.335	1363	2.5
29.98	29.979	2835	5.2
30.85	30.848	2642	4.8
31.12	31.121	4001	7.3
31.96	31.961	1156	2.1
32.82	32.815	2220	4
33.55	33.549	2879	5.3
34.52	34.515	634	1.2
35.48	35.477	1388	2.5

TABLE 8-continued

XRPD peak list of Form θ			
2 θ	d spacing, A $^\circ$	Count	%
36.01	36.005	2078	3.8
36.75	36.752	441	0.8
37.65	37.653	1361	2.5
38.53	38.534	475	0.9
39.84	39.838	946	1.7

Differential scanning calorimetry is performed using a TA Instruments Q10 DSC. Typically, samples are placed in unsealed, covered hermetic alodined aluminum sample pans and scanned from about 30 $^\circ$ C. to about 300 $^\circ$ C. at a rate of about 10 $^\circ$ C./min under a nitrogen purge of about 50 mL/min.

Differential scanning calorimetry is performed on representative samples of morphine sulfate Forms α , β , γ , δ , ϵ , ζ , η and θ , as shown in FIGS. 11, 12, 13, 14, 15, 16, 17 and 18, respectively. Two thermal events may be observed in the differential scanning calorimetry thermogram for morphine sulfate Form α at about 117 $^\circ$ C. and about 173 $^\circ$ C. Two thermal events may be observed in the differential scanning calorimetry thermogram for morphine sulfate Form β at about 112 $^\circ$ C. and about 177 $^\circ$ C. Two thermal events may be observed in the differential scanning calorimetry thermogram for morphine sulfate Form γ at about 140 $^\circ$ C. and about 234 $^\circ$ C. Three thermal events may be observed in the differential scanning calorimetry thermogram for morphine sulfate Form δ at about 58 $^\circ$ C., 136 $^\circ$ C. and about 221 $^\circ$ C. One thermal event may be observed in the differential scanning calorimetry thermogram for morphine sulfate Form ϵ at about 160 $^\circ$ C. Two thermal events may be observed in the differential scanning calorimetry thermogram for morphine sulfate Form ζ at about 163 $^\circ$ C. and about 238 $^\circ$ C. One thermal event may be observed in the differential scanning calorimetry thermogram for morphine sulfate Form η at about 284 $^\circ$ C. Two thermal events may be observed in the differential scanning calorimetry thermogram for morphine sulfate Form θ at about 158 $^\circ$ C. and about 237 $^\circ$ C.

The present disclosure also describes pharmaceutical compositions comprising one or more of the morphine sulfate crystalline forms as herein described in association with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances. These compositions may be in dosage forms such as, but not limited to, tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, autoinjector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation.

To prepare a pharmaceutical composition of the present disclosure, any one or more of the morphine sulfate crystalline forms as herein described is intimately admixed with a pharmaceutical excipient according to conventional pharmaceutical compounding techniques, which excipient may take a wide variety of forms depending of the form of preparation desired for administration (e.g. oral or parenteral). Suitable pharmaceutically acceptable excipients include those known in the art and those yet to be discovered. Descriptions of some of these pharmaceutically acceptable excipients may be found in *The Handbook of Pharmaceutical Excipients* and the Pharmaceutical Society of Great Britain. The pharmaceutical compositions of the present disclosure may be prepared according to any method

known in the art as well as yet to be discovered improvements thereto. Methods of formulating pharmaceutical compositions have been described in numerous publications such as *Pharmaceutical Dosage Forms: Tablets, Second Edition, Revised and Expanded*, Volumes 1-3; *Pharmaceutical Dosage Forms: Parenteral Medications*, Volumes 1-2; and *Pharmaceutical Dosage Forms: Disperse Systems*, Volumes 1-2.

The oral formulations of the present disclosure may be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. The sustained release dosage forms may optionally comprise particles containing any one or more of the morphine sulfate forms as herein described. Preferably, the particles are film coated with a material that permits release of the active at a sustained rate in an aqueous medium. The film coat is chosen so as to achieve, in combination with the other stated properties, desired release properties. The sustained release coating formulations of the present disclosure should preferably be capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert and tack-free. The sustained release formulations of the present disclosure preferably slowly release the active agent(s), e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate. Sustained release dosage forms according to the present disclosure may also be prepared as osmotic dosage formulations known in the art as well as improvements thereto.

The liquid forms in which the novel compositions of the present disclosure may be incorporated for administration orally or by injectable include, aqueous solutions, suitably flavored syrups, aqueous or oil suspensions, and flavored emulsions with edible oils as well as elixirs and similar pharmaceutical vehicles. The liquid forms may include suitably flavored suspending or dispersing agents such as the synthetic and natural gums. For parenteral administration, sterile suspensions and solutions are desired. Isotonic preparations which generally contain suitable preservative are employed when intravenous administration is desired.

The formulations of the present disclosure may be formulated as a pharmaceutical suppository for rectal administration comprising a suitable suppository base, and any one or more of the morphine sulfate crystalline forms as herein described. This includes the preparation of sustained release suppository formulations as described in U.S. Pat. No. 5,215,758.

The compounds of the present disclosure may be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will be continuous rather than intermittent throughout the dosage regimen.

The present disclosure provides for a method of treating pain by administering to a subject in need thereof the dosage forms described above which contain any one or more of the morphine sulfate crystalline forms as herein described. The

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dosage of the products may be varied over a wide range. Optimal dosages and dosage regimens to be administered may be readily determined by those skilled in the art, and will vary with the mode of administration, the strength of the preparation and the advancement of the disease condition. In addition, factors associated with the particular subject being treated, including subject's sex, age, weight, diet, physical activity, time of administration and concomitant diseases, will result in the need to adjust dosages and/or regimens.

EXAMPLES

The disclosure is illustrated by the following examples.

The following examples are set forth to aid in the understanding of the disclosure, and are not intended and should not be construed to limit in any way the disclosure set forth in the claims which follow thereafter. Although illustrated and herein described with reference to certain specific embodiments, the present disclosure is nevertheless not intended to be limited to the details shown. Rather, various modifications may be made in the details within the scope and range of equivalents of the claims and without departing from the spirit of the disclosure.

Example 1

Preparation of Morphine Sulfate

Morphine Technical Alkaloid (MTA) material is combined with water and 0.5 equiv. of 50% isopropyl acetate diluted sulfuric acid. The mixture is heated to about 75° C. and cooled to about 15° C. at a rate of about 0.23° C. per minute. The resulting mixture is filtered under vacuum and washed with ethanol. The filtrate is dried at about 50° C. under vacuum. The resulting solids are determined to be morphine sulfate.

Example 2

Preparation of Morphine Free Base

About 8.43 g of morphine sulfate and about 40 mL of water are added to an Easy Max™ set at 350 RPM agitation rate. The mixture becomes clear and is then heated to about 65° C. The pH is checked and determined to be about 5. About 10 mL of pre-made solution in water of 1 M NaOH is added to the mixture. Solids are formed. About 5 mL of pre-made solution in water of 1 M NaOH is added to the mixture. The pH is checked and determined to be about 6. A few NaOH pellets are added to the mixture. Heating and stirring is continued for about 2 hours. The mixture is then cooled to about 50° C., filtered under vacuum filtration and washed several times with water. The pH of the filtrate is checked and determined to be about 13. The filtrate is dried at about 45° C. under vacuum for about 12-24 hours. The resulting solids are analyzed by X-ray powder diffraction and determined to be morphine free base.

Example 3

Preparation of Form α Using Acetone

About 200 mg of morphine free base and about 1 mL of acetone are added to a vial. Concentrated sulfuric acid is pre-diluted in isopropanol. About 49 μ L of 50% isopropyl acetate diluted sulfuric acid is added to the vial. The mixture is stirred for about 4 to 5 hours at about 20 to 26° C. The

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resulting slurry is analyzed by X-ray powder diffraction and determined to be morphine sulfate Form α .

Example 4

Preparation of Form α Using Water

About 200 mg of morphine free base and about 1 mL of water are added to a vial. Concentrated sulfuric acid is pre-diluted in isopropanol. About 49 μ L of 50% isopropyl acetate diluted sulfuric acid is added to the vial. The mixture is stirred for about 4 to 5 hours at about 55 to 65° C. The resulting solids are analyzed by X-ray powder diffraction and determined to be morphine sulfate Form α .

Example 5

Preparation of Form β Using Isopropyl Acetate

About 200 mg of morphine free base and about 1 mL of isopropyl acetate are added to a vial. Concentrated sulfuric acid is pre-diluted in isopropanol. About 49 μ L of 50% isopropyl acetate diluted sulfuric acid is added to the vial. The mixture is stirred for about 4 to 5 hours at about 20 to 26° C. The resulting solids are analyzed by X-ray powder diffraction and determined to be morphine sulfate Form β .

Example 6

Preparation of Form γ Using Acetone

About 200 mg of morphine free base and about 1 mL of acetone are added to a vial. Concentrated sulfuric acid is pre-diluted in isopropanol. About 49 μ L of 50% isopropyl acetate diluted sulfuric acid is added to the vial. The mixture is stirred for about 4 to 5 hours at about 55 to 65° C. The resulting solids are analyzed by X-ray powder diffraction and determined to be morphine sulfate Form γ .

Example 7

Preparation of Form δ Using Ethanol

About 200 mg of morphine free base and about 1 mL of ethanol are added to a vial. Concentrated sulfuric acid is pre-diluted in isopropanol. About 49 μ L of 50% isopropyl acetate diluted sulfuric acid is added to the vial. The mixture is stirred for about 4 to 5 hours at about 20 to 26° C. The resulting solids are analyzed by X-ray powder diffraction and determined to be morphine sulfate Form δ .

Example 8

Preparation of Form ϵ Using Methanol

About 200 mg of morphine free base and about 1 mL of methanol are added to a vial. Concentrated sulfuric acid is pre-diluted in isopropanol. About 49 μ L of 50% isopropyl acetate diluted sulfuric acid is added to the vial. The mixture is stirred for about 4 to 5 hours at about 20 to 26° C. The resulting solids are analyzed by X-ray powder diffraction and determined to be morphine sulfate Form ϵ .

Example 9

Preparation of Form ζ Using Water

About 200 mg of morphine free base and about 1 mL of water are added to a vial. Concentrated sulfuric acid is

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pre-diluted in isopropanol. About 49 μL of 50% isopropyl acetate diluted sulfuric acid is added to the vial. The mixture is stirred for about 4 to 5 hours at about 20 to 26° C. The resulting solids are analyzed by X-ray powder diffraction and determined to be morphine sulfate Form ζ .

Example 10

Preparation of Form η Using Ethanol/Methanol

About 200 mg of morphine free base and about 1 mL of ethanol/methanol 80:20 are added to a vial. Concentrated sulfuric acid is pre-diluted in isopropanol. About 49 μL of 50% isopropyl acetate diluted sulfuric acid is added to the vial. The mixture is stirred for about 4 to 5 hours at about 20 to 26° C. The resulting solids are analyzed by X-ray powder diffraction and determined to be morphine sulfate Form η .

Example 11

Preparation of Form θ Using Water

About 5 mg of MTA material, about 11 mL of water and a 50% solution of about 0.7 sulfuric acid equiv. are heated to about 70° C. The mixture is cooled at a rate of about 1.05° C. per minute with fast agitation (about 800 RPM) over about 2.5 hours. The resulting solids are analyzed by X-ray powder diffraction and determined to be morphine sulfate Form θ .

What is claimed is:

1. A method of making morphine sulfate Form α comprising exposing a starting material comprising morphine free base to acetone and a composition comprising sulfuric acid at a temperature in the range of about 20 to 26° C. for a time sufficient to yield morphine sulfate Form α , wherein Form α has an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at about 15.71 and about 17.08.

2. A method of making morphine sulfate Form α comprising exposing a starting material comprising morphine free base to water and a composition comprising sulfuric acid at a temperature in the range of about 55 to 65° C. for a time sufficient to yield morphine sulfate Form α , wherein Form α has an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at about 15.71 and about 17.08.

3. A method of making morphine sulfate Form β comprising exposing a starting material comprising morphine free base to isopropyl acetate and a composition comprising sulfuric acid at a temperature in the range of about 20 to 26°

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C. for a time sufficient to yield morphine sulfate Form β , wherein Form β has an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at about 15.43 and about 17.78.

4. A method of making morphine sulfate Form γ comprising exposing a starting material comprising morphine free base to acetone and a composition comprising sulfuric acid at a temperature in the range of about 55 to 65° C. for a time sufficient to yield morphine sulfate Form γ , wherein Form γ has an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at about 14.28 and about 13.21.

5. A method of making morphine sulfate Form δ comprising exposing a starting material comprising morphine free base to ethanol and a composition comprising sulfuric acid at a temperature in the range of about 20 to 26° C. for a time sufficient to yield morphine sulfate Form δ , wherein Form δ has an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at about 15.68 and about 17.03.

6. A method of making morphine sulfate Form ϵ comprising exposing a starting material comprising morphine free base to methanol and a composition comprising sulfuric acid at a temperature in the range of about 20 to 26° C. for a time sufficient to yield morphine sulfate Form ϵ , wherein Form ϵ has an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at about 14.40 and about 23.58.

7. A method of making morphine sulfate Form ζ comprising exposing a starting material comprising morphine free base to water and a composition comprising sulfuric acid at a temperature in the range of about 20 to 26° C. for a time sufficient to yield morphine sulfate Form ζ , wherein Form ζ has an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at about 14.28 and about 20.44.

8. A method of making morphine sulfate Form η comprising exposing a starting material comprising morphine free base to an ethanol/methanol mixture and a composition comprising sulfuric acid at a temperature in the range of about 20 to 26° C. for a time sufficient to yield morphine sulfate Form η , wherein Form η has an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at about 15.49 and about 14.36.

9. A method of making morphine sulfate Form θ comprising exposing a starting material comprising morphine to water and a composition comprising sulfuric acid at a temperature in the range of about 65 to 75° C. for a time sufficient to yield morphine sulfate Form θ , wherein Form θ has an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at about 14.22 and about 14.05.

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